REMARKS

Claims 1-39 were originally filed and were subject to a Restriction Requirement. Applicants affirm election, with traverse, of original claims 15-19, corresponding to the invention of Group VII, and further to the polypeptide of SEQ ID NO:6 of that group, again with traverse. Applicants submit that the invention encompassed by claims 17 and 18, drawn to SEQ ID NOs:7 and 8, respectively could be examined together with claims 15, 16 and 19, drawn to the polypeptide of SEQ ID NO:6 without undue burden. The three polypeptide sequences are sufficiently few in number to not constitute an undue burden to be searched together.

Accordingly, Applicants respectfully submit that examination of originally filed claims 15-19 would pose no undue burden. Thus, Applicants request reconsideration and withdrawal of the Restriction Requirement and examination of all claims in Group VII.

Justification for the amendments is as follows. The specification has been amended to spell out certain abbreviations, and the claims have been amended to clarify the invention. In particular, the specification has been amended to spell out the abbreviations "CYP1A1" and "BPDE" at page 2, and the term "PNAs" at page 3. Claim 15 has been amended to delete the phrase "a portion thereof" and oligopetides recited in step (b). Applicants do not concede to the Patent Office position for reasons cited below in response to the rejection of claims; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. No new matter is added by any of these amendments, and entry of the amendments is requested.

Information Disclosure Statement

The Examiner acknowledged Applicants IDS from the parent case, Serial Number 09/386,493, but stated that after reviewing the parental application, references NO: 1, 4, 5 and 9 of the IDS were not found and invited applicant to submit such documents. The cited references are attached to this response.

Objection to the Specification

The Examiner stated that the term CYP1A1 in p. 2, line 23 needs to be spelled out fully for the first time; see also p.2, line 26 (BPDE" and p. 3, line 22 "PNAs". Correction is required. The terms CYP1A1, BPDE, and PNAs have been spelled out in the specification.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 15, 16 and 19

The Examiner has rejected claims 15, 16 and 19 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the instant application claims an oligopeptide comprising at least 6 sequential amino acids of SEQ ID NO:6, however, that the claim as written encompasses a broad genus of the variant polypeptide and immunogenic fragments. The Examiner stated that adequate written description of the invention may be shown by disclosure of sufficient, relevant, identifying characteristics (i.e., structure and chemical/physical properties) so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. Because the instant application includes a large quantity of variations (species of the genus), a requirement for sufficient description of variety of the variants, i.e., species, must be met in order to reflect that variation.

Applicants Response

Applicants submit that an oligopeptide "having at least 6 sequential amino acids of SEQ ID NO:6" is readily determined by one skilled in the art given the amino acid sequence of SEQ ID NO:6, such that no further structural or chemical property of the claimed oligopeptide need be given to determine its' composition. The mere fact that a genus may be large does not, in itself, necessarily convey to one skilled in the art that the applicant may not be in possession of it, particularly when the genus is so clearly defined as the instant case, and the structure of the parent molecule from which it is derived (SEQ ID NO:6) is completely disclosed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical

> and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art. The derivation of any given oligopeptide of SEQ ID NO:6 is conventional and well known in the art given the sequence of SEQ ID NO:6 which is specifically disclosed.

Likewise, an immunogenic fragment of SEQ ID NO:6 is also readily determined given the structure of the protein from which it is derived and the knowledge of one skilled in the art to determine such fragments within the parent molecule. The derivation of immunogenic fragments from the claimed protein sequences is specifically described in Example VIII, pp. 22-23 of the instant application "Production of Specific Antibodies". In particular, the specification states in the last paragraph at p. 22, bridging p. 23 that "...the amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art".

Therefore one skilled in the art would clearly know how to determine the claimed oligopeptide and immunogenic fragments of SEQ ID NO:6 given the sequence structure of SEQ ID NO:6, the teachings of the specification, and the knowledge of one skilled in the art, and are therefore sufficiently described to convey to one skilled in the art that applicant was in possession of them. However, in the interest of expediting prosecution and the allowance of claims, the term "oligopeptide" and the phrase "portion thereof" have been deleted from the claims.

The Examiner stated that although the application has provided a description of isolation and identification of the polynucleotide encoding SEQ ID NO:6 protein and description of the sequence of the purified proteins encoded thereby, the application insufficiently describes the biological and therapeutic role of this protein or its significance. The instant specification sets forth an agonist and antagonist of the protein that may be administered to a subject to treat or prevent a disease induced through exposure to PHA compounds, however, all the above mentioned therapeutic uses are directed to a protein sequence, PSEQ, that embraces exceptionally-divergent proteins SEQ ID NOs:6, 7 and 8, which are distinct in their primary structure, posttranslational modification and interactions with cell signaling pathways. Thus, the

Examiner stated, the uses of the claimed protein SEQ ID NO:6 is not specifically disclosed and described by the specification.

Applicants Response

Applicants disagree that the use of the claimed protein of SEQ ID NO:6 is not specifically disclosed and described in the specification. In particular, the use of the claimed polypeptides, including SEQ ID NO:6 in the production of antibodies for the diagnosis of diseases characterized by over-or-under expression of the protein is fully enabled. The instant application identifies the polynucleotide encoding SEQ ID NO:6 as the human homolog of a rat gene overexpressed in rat liver in response to a genotoxic agent, benzo(a)pyrene (PAH), and that this sequence is therefore useful in the diagnosis of diseases associated with PAH induction, such as cancer. See Table 1 and the specification, at p. 9, lines 18-21. The specification specifically discloses at p. 15, lines 23-25, that "antibodies or antibody fragments comprising an antigen binding site that specifically binds PSEQ may be used for the diagnosis of diseases characterized by the over-or-under expression of PSEQ". PSEQ itself is defined as referring to a protein of the present invention, including SEQ ID NO:6. See specification at p. 6, lines 11-12. The use of the protein of SEQ ID NO:6 or immunogenic fragments of SEQ ID NO:6 for the production of said antibodies is enabled as described previously in this response. Therefore, the use of the protein of SEQ ID NO:1 in the production of antibodies specific for identifying the expression of SEQ ID NO:1 in the diagnosis of a cancer, or the predisposition to cancer, is fully enabled by the specification. Furthermore, such a use does not require any knowledge of the biological activity of the protein or its interactions with cell signaling pathways.

The Examiner stated that the specification provides an expression profile for the human polynucleotide SEQ ID NO:1 encoding the disclosed protein SEQ ID NO:6 in response to exposure to a BP-compound in various tissues, however that this does not necessarily reflect that the expressed protein level will be directly proportional to the extent of the exposure to BP-compound as evidenced by: 1) none of the expression profiles particularly represented are compared to BP-untreated tissues; 2) BP-treatment mediates multiple expressions of distinct and/or different mRNA species (see Table 1); and 3) polynucleotide expression does not necessarily manifest cellular level of the expressed protein. Therefore, the Examiner stated, applicant sets forth a substantially purified protein, however applicants provide no factual evidence with respect to the substantially purified protein and the purified protein mediated or directed uses in therapeutics or diagnostics.

Applicants Response

Applicants disagree that the specification does not provide factual evidence for a diagnostic use of the claimed protein, SEQ ID NO:6, for the reasons discussed previously (See Applicants Response, p. 12, above). With respect to item 1) above, applicants submit that the Examiner misinterprets the purpose of presentation of the human tissue expression profile in the last column of the table. The data of Table 1

establishes the human sequences of SEQ ID NOs:1-5 as potential markers for cancer, or cancer-predisposition in tissues in which they are overexpressed by virtue of their identity with corresponding rat genes that are expressed in adult rat liver in response to BP, but absent from untreated, control rat liver, e.g., are overexpressed in response to BP treatment. See specification, at p. 5, lines 19-20. The identification of specific tissues in which the human genes are expressed, such as the predominate expression of SEQ ID NO:1 in reproductive tissues (Table 1), provides a specific marker in that tissue for cancer, or cancer predisposition, because there is a substantial likelihood that increased expression, or over expression, of the gene in that tissue as determined by comparison with established control levels is indicative of cancer, or cancer predisposition. With respect to 2), above, applicants submit that the induction of multiple, distinct and/or different mRNA species by BP is irrelevant to the value of any one of the induced genes, such as SEQ ID NO:1 or its encoded protein, as a marker for the purposes claimed, only that the mRNA transcript and its encoded protein are most likely expressed at similar or proportional levels. This issue, the Examiner addresses in item 3). However, the Examiner presents no evidence or sound scientific reasoning why one skilled in the art would doubt that mRNA expression is not indicative of protein expression in most cases, in particular, the instant case. Applicants submit that it is well known in the art that while steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (pages enclosed):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... For most genes, this is a major control point; probably it is the most common level of regulation. [page 847, emphasis added].
>
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation. [pages 847-848, emphasis added]

Thus the question is not whether applicant has provided factual evidence of protein expression in the instant case, but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:6 expression correlates with the levels of SEQ ID NO:1 mRNA. Applicants need only prove a "substantial likelihood" of utility, and hence of enablement; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). It is the burden of the Examiner to prove otherwise. In the

case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:6 were controlled by anything other then mRNA transcription, thereby dismissing the significance of mRNA levels.

For all the above reasons, applicants submit that the claimed polypeptide, SEQ ID NO:6, and immunogenic fragments thereof are sufficiently described in the specification to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention, and therefore request withdrawal of the rejection of claims 15, 16 and 19 under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 15, 16 and 19

The Examiner has rejected claims 15, 16 and 19 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for construction of BP-treated rat liver cDNA library (pages 18-19) and the isolation of the cDNA clones (pages 19-20), expression analysis using electronic subtraction to create a transcript profile (pages 20-21), labeling the isolated polynucleotides for hybridization analysis (pages 21-22), antibody production, etc., the specification does not enable one of skill in the art to make and use the invention commensurate with the scope of the claims.

Since applicants have deleted reference to "oligopeptide" in the claims for the reasons previously discussed, only the Examiners' comments regarding the polypeptide itself, SEQ ID NO:6, or immunogenic fragments thereof, or compositions thereof will be reiterated and addressed.

The Examiner stated (at p. 9) that the claims are directed to a purified polypeptide that can be used a pharmaceutical composition formulated with a pharmaceutically acceptable carrier in order to evaluate and identify environmental pollutants and pollutant mediated diseases or disorders, however, that the specification does not provide a working example, teaching, direction or guidance as to the chromatographic purification of the protein as claimed and use of the purified protein as a pharmaceutical composition.

Applicants Response

Methods of protein isolation and purification are old and well understood in the art and therefore need not be described in the instant application. A specification need not describe---and best omits---that which is well known in the art. See, e.g., In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed Cir 1991). Applicants furthermore point out that claim 19 recites "A composition comprising a protein of claim 15 and a pharmaceutical carrier", not a "pharmaceutical composition". The term "composition" as it is broadly used in the specification and understood in the art is not limited to pharmaceutical compositions for therapeutic use, but encompass the use of buffers, salts, etc. to provide compositions suitable for storage and stability of biological materials, such as a protein. Thus the use of a composition such as that recited in claim 19 may be, for example, for stable storage of the polypeptide.

The Examiner stated (at p. 12) that applicants are not in possession of any immunogenic fragments of the polypeptide of SEQ ID NO:6, since the specification provides no teachings, direction and working examples in regard to preparation of any fragments and testing for their immunogenicity. It would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:6 would be selected for --- raising antibodies for diagnostic assay, and to establish which subsequence would be used to formulate the peptide subsequence with a pharmaceutical carrier in order for developing a pharmaceutical composition ---. The Examiner stated (at p. 13) that the general knowledge and level of one skilled in the art do not supplement the omitted description because specific, not general, guidance is needed. Immunogenic fragments and pharmaceutical compositions of the peptide/proteins are highly variant. The Examiner further discussed aspects of antibody epitope recognition that are determining factors for affinity, specificity and valency with respect to antibody-antigen interaction.

Applicants Response

The teachings of the specification for identifying immunogenic fragments of SEQ ID NO:6---including references and tools available in the art---are found specifically in Example VIII, pp. 22-23 of the specification. As stated in that example, "Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art". Such techniques, though generally applicable to proteins may be specifically applied to the instant protein. Thus, again, what is well known in the art need not be described in detail in the specification. The number of immunogenic fragments suitable for obtaining an antibody specific for SEQ ID NO:6 using these methods, would necessarily be limited and not require "undue experimentation" as the Examiner suggests.

For all of the above reasons, as well as those presented in response to the previous rejection of these claims under 35 U.S.C. § 112, first paragraph regarding possession, applicants submit that claims 15, 16 and 19, as amended, are fully enabled by the specification, and request withdrawal of the rejection of claim 15, 16 and 19 under 35 U.S.C. § 112, first paragraph.

35 U.S.C § 112, Second Paragraph, Rejection of Claims 15, 16 and 19

The Examiner has rejected claims 15, 16 and 19 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards and the invention. In particular, the Examiner stated, claim 15 is unclear as "a portion thereof". Applicants submit that the phrase "portion" is both well understood in the art and specifically defined in the specification at p. 7, lines 16- 18, where it states that "Portion", as used herein, refers to any part of a protein used for any purpose, but especially for the screening of a library of molecules which specifically bind to that portion or for the production of antibodies". However , as stated previously the phrase "a portion thereof" has been deleted from the claim, and withdrawal of the rejection is therefore requested.

35 U.S.C. 102(b), Rejection of Claims 15 and 16

The Examiner has rejected claims 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Kikuno et al. (DNA Res, 1999, 6:197-205). The Examiner stated that a polypeptide which is encoded by a cDNA clone (Accession number: AB029032) encodes a polypeptide of 1,957 amino acids, the C-terminal portion of which (aa 1371-1957) is 100% identical to the instant SEQ ID NO:6.

Applicants first of all remind the Examiner that the instant application is a divisional application of USSN 09/386,493, filed August 30, 1999. As the attached NCBI PubMed citation of the Kikuno article shows, the earliest possible publication of the cited reference is June 30, 1999, which would only constitute potential prior art under 35 U.S.C. 102(a). Accordingly applicants submit a declaration under 37 CFR 1.131 signed by all of the inventors showing conception of the claimed invention and diligence in reduction to practice of the claimed invention from a time prior to the critical date of the cited reference to the filing date of the parent application. Applicants therefore submit that Kikuno et al do not anticipate SEQ ID NO:6 or an immunogenic fragment of SEQ ID NO:6 and request withdrawal of the rejection of claim 15 under 35 U.S.C. § 102(a).

35 U.S.C § 103(a), Rejection of Claims 15, 16 and 19

The Examiner has also rejected claims 15, 16 and 19 under 35 U.S.C. § 103(a) as unpatentable over Kikuno in view of Cunningham et al.(US Patent No. 6372431). The teachings of Kikuno et al. are supra. The Examiner stated that Kikuno et al. do not teach a composition comprising SEQ ID NO:6 and a pharmaceutical carrier, however, Cunningham et al. teach a pharmaceutical (composition) comprising a substantially purified mammalian protein used in diagnostic and therapeutic applications including detecting toxicological responses. The Examiner stated that it would have been obvious for one skilled in the art at the time the application was filed to combine the teachings of Kikuno et al. with those of Cunningham et al. to produce a composition comprising a protein of SEQ ID NO:6 and a pharmaceutical carrier.

Kikuno et al. has been dismissed as prior art to the claimed sequence of SEQ ID NO:6 under 35 U.S.C. § 102(a) for the reasons cited in the response to rejection of claims under that section, above. Cunningham et al. do not teach or suggest the sequence of SEQ ID NO:6. Applicants submit that for there to be a proper *prima facie* case of obviousness under 35 U.S.C. § 103(a), the reference, or combination of references, must teach or suggest all the claim limitations. Since Cunningham et al. do not teach or suggest the sequence of SEQ ID NO:6, there can be no proper *prima facie* case of obviousness against claims 15, 16 and 19, and applicants therefore request withdrawal of the rejection of claims under 35 U.S.C. § 103(a).

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited. If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent of Record, below. Applicants further request that, upon allowance of claim 15, that claims 20, 21, and 23 be rejoined and examined as methods of use the composition of matter of claim 15 that depend from and are of the same scope as claim 15 in accordance with *Ochiai and Brouwer*. See MPEP § 821.04 and the Commissioner's Notice in the Official Gazette of March 26, 1996.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Paragraph beginning at line 17 of page 2 has been amended as follows:

There is growing evidence that predisposition to cancer may reside in polymorphic genes involved in carcinogen metabolism and repair. One major goal of epidemiologists is the identification of individuals who are exposed to high levels of carcinogen, carry cancer-predisposing genes, and lack protective factors. A combination of cancer-predisposing genes could be used as an intermediate risk marker rather than taking diagnosis of cancer as the endpoint. Such markers may include PAH-DNA adduct level and polymorphism in PAH-metabolizing enzymes such as the cytochrome P450 family member, cytochrome P4501A1, (CYP1A1), the 4 S PAH-binding protein glutathione S-transferase (GSTM1), and cAMP-dependent protein kinase (Bhat et al. (1996) J. Biol. Chem. 271:32551-32556; and Bartsch, H. et al. (1998) Recent Results Cancer Res. 154:86-96). For example, Bartsch et al. (supra) showed that (+)-anti-benzo[a]pyrene diol-eoixide (BPDE)-DNA adduct levels in [broncial] bronchial tissues of cigarette smokers with high CYP1A1 inducibility and inactive GSTM1 were approximately 100-fold higher than in smokers with an active GSTM1.

Paragraph beginning at line 17 of page 3 has been amended as follows:

The invention additionally provides methods for using a nucleic acid molecule. One method uses the nucleic acid molecule to screen a library of molecules or compounds to identify at least one ligand which specifically binds the nucleic acid molecule and comprises combining the nucleic acid molecule with a library of molecules or compounds under conditions to allow specific binding and detecting specific binding, thereby identifying a ligand which specifically binds the nucleic acid molecule. In this first method, the library is selected from DNA molecules, RNA molecules, peptide nucleic acids (PNAs), mimetics, and proteins; and the ligand identified using the method may be used to modulate the activity of the nucleic acid molecule. A second method uses the nucleic acid molecule to purify a ligand which specifically binds the nucleic acid molecule and comprises combining the nucleic acid molecule with a sample under conditions to allow specific binding, detecting specific binding between the nucleic acid molecule and a ligand, recovering the bound nucleic acid molecule, and separating the nucleic acid molecule from the ligand, thereby obtaining purified ligand. A third method uses the nucleic acid molecule to diagnose a disease or condition associated with the altered expression of a gene that is expressed in response to PAH in a plurality of biological samples and comprises hybridizing a nucleic acid molecule to